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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/755,747	01/05/2001	Anthony J. Brookes	78104.017	3891

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	11

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/755,747	BROOKES, ANTHONY J.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 22, 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *53-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The rejection under 35 U.S.C. 102(b) as being anticipated by Ririe et al is withdrawn in view of the amendment.

2. The rejection of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47 and 49 under 35 U.S.C. 102(e) as being anticipated by Wittwer et al is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-6, 8, 10-19, 21, 23-32, 34, 36-45, 47 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drobyshev et al (Gene (1997) 188:45-52) in view of Wittwer (U.S. Patent 6,174,670).

Drobyshev teaches a method of detecting DNA variation by monitoring the formation or dissociation of a of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here the 10 mer oligonucleotide attached to the solid support which is a solid surface as broadly interpreted (page 46, column 2, subheading "oligonucleotide microchip"),

(b) an oligonucleotide specific for the single stranded DNA sequence specific for one allele of the variation and capable of hybridizing to the single strand (a) to form a

duplex (here the RNA transcript (page 46, figure 1 and page 47, subheading "RNA samples")

(c) a marker detection of the duplex structure of (a) plus (b) which forms a complex with the said duplex (here the fluorescent labels fluorescein and rhodamine (page 51, column 1),

which method comprises:

(1) continually measuring an output signal indicative of the duplex formed from the strand (a) and probe (b) (see page 49, figure 2) and

(2) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page 49, figure 2).

Drobyshev further teaches formation of two or more complexes, each with a probe specific for a different allele of the variaition, and observing their respective denaturing or annealing conditions to distinguish alleles of the variation (page 49, figure 2).

Drobyshev does not teach the use of a marker which is duplex specific in the analysis.

Wittwer et al teaches a method of detecting DNA variation by monitoring the formation or dissociation of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here denatured genomic DNA (column 9, line 21) and/or denatured amplified PCR products, including an 81 basepair cystic

fibrosis gene product (column 40, lines 58-67)) as well as many longer PCR products such as the 536 base pair b-globin sequence (column 47, line 24),

(b) an oligonucleotide specific for the single stranded DNA sequence (here either the primers used in PCR (column 41, lines 1-20) or pairs of fluorescently labeled oligonucleotide probes (column 9, lines 27-37)),

(c) a marker specific for the duplex structure of (a) plus (b) which forms a complex with the said duplex and reacts uniquely when interacting within the duplex (here either SYBR green, (see column 40, line 65) or the fluorescence resonance energy transfer pair of labels, which differentially fluoresce when in duplex or single stranded states (column 9, lines 27-37)),

which method comprises:

(1) continually measuring an output signal indicative of interaction of the marker with duplex formed from the strand (a) and probe (b) (see column 9, lines 50-55 or column 41, lines 14-17 and figure 43) and

(2) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page column 9, lines 55-59 or column 41, lines 14-17 and figure 43).

Column 14 details a similar assay for differentiating the Factor V Leiden mutation. Column 46 teaches the use of two or more complexes of the kind defined, each with a probe specific for a different allele of the mutation which multiple detection probes are distinguished by the different melting peaks (see column 46, lines 49-61).

Wittwer further teaches measurement of the annealing based upon the first or second derivatives of the fluorescent melting curves (column 12 and columns 23-26) and expressly discusses measurement of the second order rate constant (see column 12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the markers of Wittwer in the mutation detection method of Drobyshev since Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)". Thus, an ordinary practitioner would have been motivated to use SYBR™ Green I in the melting curve analytical method of Drobyshev since Wittwer teaches that this intercalator is superior in sensitivity, is useful in the particular assay employed by Drobyshev and is inexpensive.

3. Claims 1-8, 10-21, 23-34, 36-47 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drobyshev et al (Gene (1997) 188:45-52) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Heller et al (U.S. Patent 6,048,690).

Drobyshev in view of Wittwer teach the limitations of claims 1-6, 8, 10-19, 21, 23-32, 34, 36-45, 47 and 49-52 as discussed above. Drobyshev in view of Wittwer do not teach immobilization of the oligonucleotide using biotin-streptavidin.

Heller teaches immobilization of oligonucleotides to arrays using biotin-streptavidin for nucleic acid detection assays (column 16, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Heller in the detection method of Drobyshev in view of Wittwer since Heller states "In this example, the first probe (a capture/quencher probe sequence) has two terminal functional groups, a 5'-terminal biotin group which allows the probe to be immobilized to the surface (permeation layer) of a microlocation test site on an active DNA chip or other hybridization device." (column 16, lines 62-67). An ordinary practitioner would have been motivated to use the biotin capture method in order to permit immobilization of probes to desired microlocations of DNA chips for the analytical method. Also, an ordinary practitioner would be motivated to select a known equivalent of the method of Drobyshev for attachment of the nucleic acids to the array as Drobyshev notes a variety of attachment mechanisms (page 45, column 2).

4. Claims 1-6, 8-19, 21-32, 34-45 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drobyshev et al (Gene (1997) 188:45-52) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Konrad et al (U.S. Patent 5,789,167).

Drobyshev in view of Wittwer teach the limitations of claims 1-6, 8, 10-19, 21, 23-32, 34, 36-45, 47 and 49-52 as discussed above. Drobyshev in view of Wittwer do not teach the use of Hepes buffer in hybridization.

Konrad teaches that " The conditions for hybridization of oligonucleotide sequences are well known. Generally, the hybridization step is either performed in a buffered aqueous salt solution at high temperature or in the presence of formamide at lower temperature. The aqueous, high temperature procedure is typically carried out

in a Tris buffer, such as 0.3M NaCl, 20 mM Tris -HCl, pH 6.8, at 67.degree. C. Other buffering systems such as hepes or glycine-NaOH and potassium phosphate buffers can be used. (column 14, lines 59-67)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Hepes buffer of Konrad in the detection method of Drobyshev in view of Wittwer since Konrad expressly teaches that Hepes buffer is an equivalent buffer for use in hybridization reactions.

Response to Arguments

5. Applicant's arguments filed July 22, 2002 have been fully considered but they are not persuasive.

While the Wittwer 102 rejection is withdrawn, Applicant makes one argument which remains relevant to the 103 rejections. Applicant argues that Wittwer does not teach a complex consisting of a single stranded DNA, oligonucleotide and marker. This is not correct because it fails to interpret the claims using the broadest reasonable interpretation. In the method of Wittwer, it is absolutely clear that Wittwer has, when the PCR reaction is denatured, single strands, and the SYBR green marker present. The claim does not limit the probe to any length or structure. Thus, the second strand synthesized in the PCR reaction can constitute the probe and Wittwer teaches the necessity of such a strand to analyze the sequence for determination of the variation. Thus, Wittwer expressly teaches this element.

Applicant first argues that there would not be motivation to use SYBR green in the methods of Drobyshev. This argument is not found persuasive because Drobyshev

expressly monitors hybridization by measurement of melting curves, just as Wittwer does, and the advantages disclosed by Wittwer in the use of SYBR green would be directly applicable and expected to apply to the Drobyshev method. Applicant incorrectly states that Drobyshev is limited to DNA/RNA duplexes. In fact, Drobyshev also uses the corresponding DNA 19 mers, which are DNA molecules (see page 49, column 1) and would result in a DNA/DNA duplex. Specific and substantial motivations to combine these methods, which are both directed toward the same problem of analyzing melting curves of nucleic acids, are presented in the rejection as discussed in the rejection above.

Further, the argument is not relevant to the current claims because the claims include no limitations that the duplex be a DNA/DNA duplex since the oligonucleotide can be a DNA analogue and RNA is such an analogue. While applicant later states that the claims are limited to DNA homoduplexes, this is not consonant with the actual claim language which permits DNA analogues that would include RNA.

As a separate point, since hybridization of either DNA or RNA operates by the same mechanism and since SYBR green interacts with both DNA and RNA (see Spiess et al (Biotechniques (1999) 26:46-48 attached for evidence of interaction of SYBR green with RNA).

It is noted that Applicant has amended the claim to require the DNA strand to be bound to a solid surface. Applicant argues that a polyacrylamide gel support is not a solid surface. While the specification supports the phrase "solid surface", the specification does not define or limit this term in any way. That a Polyacrylamide gel

can be considered a solid surface by the skilled artisan is evidenced by Patent Publication 2002/0109841, which states "on a two dimensional surface such as a glass microscope slide, polyacrylamide gel, silicon microarray, or other solid surfaces . (see column 4, lines 2-4)". Thus, contrary to Applicant's interpretation, which limits a solid support surface to not include a polyacrylamide gel, the art clearly recognizes such a gel as an equivalent and as a solid surface.

Applicant then argues the rejection with regard to Heller. Applicant argues Heller alone, without combining the teachings of Drobyshev and Wittwer. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Heller is relied upon solely to teach that biotin-streptavidin binding to surfaces is a desirable and well known method for immobilization of nucleic acids onto solid surfaces.

Applicant similiarly argues the rejection further in view of Konrad without combining the references. Recognition of equivalents is a well known basis for substitution. As MPEP 2144.06 notes "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art." Here, the prior art reference of Konrad, cited for the rejection, expressly states that Tris and Hepes are known equivalents. MPEP 2144.06 continues to state "An express suggestion to substitute one equivalent component or process for another is not

necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

September 3, 2002